

## Phase I Trial: Cirtumzumab Inhibits ROR1 Signaling and Stemness Signatures in Patients with Chronic Lymphocytic Leukemia.

**Journal:** Cell Stem Cell

**Publication Year:** 2018

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**PubMed link:** 29859176

**Funding Grants:** A Phase 1b/2a Study of the ROR1-Targeting Monoclonal Antibody, Cirtumzumab, and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in B-Cell Cancers

### Public Summary:

Cirtumzumab is a drug that was developed through support by the California Institute of Regenerative Medicine to specifically bind and inhibit ROR1 on cancer cells. ROR1 is an attractive target for a new therapy to treat patients with cancer because it is expressed on cancer cells, but not on normal post-partum tissues. Previous studies have determined that cirtumzumab binds specifically to ROR1 and blocks Wnt signaling, which is important in cancer and cancer stem cells. We report the results of a Phase 1 clinical trial to evaluate the safety and activity of this Cirtumzumab in 26 patients with chronic lymphocytic leukemia (CLL), a disease with high expression of ROR1. Cirtumzumab was well-tolerated, without any severe toxicities. Patients did not experience weight loss, pancreatitis, hyperglycemia, or other drug-dependent toxicities, consistent with the notion that cirtumzumab does not bind to normal tissues. We confirmed that ROR1 was blocked in the leukemic cells, based on decreased levels of some intermediary molecules, HS1 and Rac1. Strikingly, we found that the overall genetic signature of the leukemic cells was significantly modified by cirtumzumab. Prior to treatment, the leukemia cells turned on genes in a manner resembling stem-cells; this was reversed by cirtumzumab and the leukemic cells became more similar to normal blood cells. The majority of treated patients had stable disease with remissions that were durable without subsequent therapy for a median of 8.6 months. In summary, the results support further development of cirtumzumab as a specific and safe inhibitor of ROR1/Wnt signaling, and the safety profile of cirtumzumab makes it an ideal agent to combine with other therapies. A phase 1b/2 combination clinical trial has been initiated based on these findings in patients with CL, lymphoma, breast cancer, and other intractable cancer-stem-cell-driven cancers in which ROR1 is implicated.

### Scientific Abstract:

Cirtumzumab is a humanized monoclonal antibody (mAb) that targets ROR1, an oncoembryonic orphan receptor for Wnt5a found on cancer stem cells (CSCs). Aberrant expression of ROR1 is seen in many malignancies and has been linked to Rho-GTPase activation and cancer stem cell self-renewal. For patients with chronic lymphocytic leukemia (CLL), self-renewing, neoplastic B cells express ROR1 in 95% of cases. High-level leukemia cell expression of ROR1 is associated with an unfavorable prognosis. We conducted a phase 1 study involving 26 patients with progressive, relapsed, or refractory CLL. Patients received four biweekly infusions, with doses ranging from 0.015 to 20 mg/kg. Cirtumzumab had a long plasma half-life and did not have dose-limiting toxicity. Inhibition of ROR1 signaling was observed, including decreased activation of RhoA and HS1. Transcriptome analyses showed that therapy inhibited CLL stemness gene expression signatures in vivo. Cirtumzumab is safe and effective at inhibiting tumor cell ROR1 signaling in patients with CLL.

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